~~32.~~ 95. (New) The method of claim ~~92~~ 31, wherein the adjuvant is aluminum hydroxide.

~~33.~~ 94. (New) The method of claim 90, 29 wherein said antibody is administered in an amount of about 1 mg to about 4 mg.

C ~~34.~~ 95. (New) ~~The~~ THE ~~he~~ method of claim 90, 29 wherein said antibody is administered in an amount of about 1 mg.

~~35.~~ 96. (New) The method of claim 90, 29 wherein said antibody is administered in an amount of about 2 mg.

~~36.~~ 97. (New) The method of claim 90, 29 wherein said antibody is administered at weekly intervals.

C ~~37.~~ 98. (New) The method of claim 90, 29 wherein said antibody is administered ~~every two~~ at bi-weekly intervals. ~~weeks~~.

B Cancel. ~~38.~~ 99. (New) The method of claim 90, 29 wherein said antibody is heat-treated prior to administration.

REMARKS

Claims 62-89 were pending in the present application. Claims 64-67 and 78-81 were previously withdrawn from consideration as being drawn to non-elected invention. By virtue of this response, new claims 90-99 have been added. Accordingly, claims 62-63 and 68-77 and 82-99 are currently under examination. Applicants acknowledge the election of species of melanoma, which should likewise apply to the newly submitted claims. Support for new claims

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90-91 is found throughout the specification at, *inter alia*, page 8, lines 3-6; and pages 28-33. Support for new claims 92-93 is found throughout the specification at, *inter alia*, page 14, lines 3-4; page 54, lines 15-16; and Examples 3-5. Support for new claims 94-96 is found throughout the specification at, *inter alia*, page 60, line 24 to page 61, line 2. Support for new claims 97-98 is found throughout the specification at, *inter alia*, page 61, lines 11-13. Support for new claim 99 is found throughout the specification at, *inter alia*, page 54, lines 15-16.

Attached hereto is a marked up version of the changes made to the claims and specification by the current amendment with additions underlined and deletions bracketed. The attached pages are captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

Concerning the drawings

Applicants acknowledge the Examiner's statement that the declaration of S. Chatterjee is deemed sufficient to explain the changes to the Figures (as previously submitted on 4/15/1999). Applicants will address under separate cover the Examiner's concern that the drawing correction submitted 4/15/1999 was not in the form of a pen-and-ink sketch showing changes in red ink or with the changes otherwise highlighted.

Concerning the specification

Applicants acknowledge the Examiner's entry of the amendment filed 4/15/99 to the specification on page 12, lines 12-23. However, Applicants do not agree with the Examiner's assertion that the amendment did not need brackets or underlining. The Examiner cited MPEP 714.22(a)(1)(iii) in support of this assertion. This section of the MPEP states that "Matter deleted by amendment can be reinstated only by a subsequent amendment presenting the *previously* deleted matter as a new insertion" (emphasis added). Applicants note that this section refers to reinstatement of previously deleted matter. In the instant case, Applicants indicated

deletion of *existing* text by brackets and insertion of corrected text by underlining, which Applicants believe to be an acceptable manner of making amendments on 4/15/1999.

The Examiner alleges that it is unclear why the numbers are bolded in the amendment filed 4/15/1999 to page 85 line 4 to page 86 line 5. With this Amendment, Applicants have amended the specification as previously amended to un-bold the previously bolded text.

With this Amendment, the current status of all U.S. applications has been updated.

Concerning the Information Disclosure Statement

Applicants acknowledge the Examiner's request that Applicants supply copies of the references listed as 23-102 on the PTO-1449 submitted on April 15, 1999. Applicants will address this request under separate cover.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 75 and 89 are rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner alleges that the meaning of the phrase "said antibody is heat-treated prior to administration" is not clear, apparently because it is allegedly not clear what temperature is intended or what is "heat-treating an antibody." Office Action, page 4.

Applicants respectfully traverse.

Applicants respectfully submit that one skilled in the art would understand what is meant by "said antibody is heat-treated prior to administration." Indeed, the specification teaches that a vaccine composition comprising 1A7 can be incubated to, for example, about 48°C. Specification page 54, lines 15-16. Applicants respectfully submit that one skilled in the art would know what temperature(s) would be appropriate in the context of functional embodiments of instant claims 75 and 89, which are directed to a method of delaying recurrence and a method of delaying development of a GD2-associated tumor in an individual, respectively. Further in this context, Applicants respectfully submit that the meaning of the phrase "heat-treating an

antibody" would be evident to one skilled in the art. Thus, Applicants respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 62, 63, 68-75 and 89 are rejected because the specification allegedly fails to enable a method of delaying the recurrence of melanoma in an individual. The Examiner also alleges that the specification fails to teach heating the 1A7 antibody to any temperature other than 48°C for 30 minutes prior to administration. The Examiner further suggests that no evidence has been provided to indicate that 1A7 would lessen the recurrence of melanoma in an individual, citing Gura et al. (*Science* (1997), 278:1041-1042) in support of the Examiner's contention regarding the criticality of a working example. Office Action, page 6.

Applicants respectfully traverse.

The specification amply teaches how to make and use the claimed invention. Preparation of the 1A7 antibody and 1A7 polypeptides comprising the light and heavy chain variable region sequences contained in SEQ ID NO:2 and SEQ ID NO:4 is described in the specification at pages 24-25, 28-37, 48-50, and in Examples 1, 2, 6-7. Methods of using the 1A7 and 1A7 polypeptides to achieve the claimed invention, including methods of administration and determining effects of administration, are described in the specification at pages 38-40, 51, 55-65, and in Examples 3-5, 8-10. Thus, the specification amply provides teachings that enable the claimed invention.

In support of Applicants' position, Applicants submit herewith a Declaration by Dr. Kenneth Foon. According to Dr. Foon, in one clinical study wherein melanoma patients were administered 1A7 in accordance with the teachings of the specification, the median survival duration was at least 16 months, which is superior to those reported from other phase II trials in which the expected survival durations are typically in the range of 5 to 10 months. Most notably, one patient had a complete response, and 12 patients were stable from 14 to 37+ months. Declaration by Dr. Kenneth Foon, paragraphs 4-5. Dr. Foon also declares that in another clinical

study in which patients were administered 1A7 in accordance with teachings of the specification, the overall survival and relapse-free survival durations of melanoma patients in the adjuvant setting were found to be comparable to those of melanoma patients who were administered high dose interferon Alfa-2b (HDI); HDI has previously been reported to be beneficial for treating melanoma patients. Declaration by Dr. Kenneth Foon, paragraphs 5-6. The patients in this clinical study had had curative resection of the primary lesion and lymph node metastases, and had no evidence of distant metastases on bone scan, or computed tomography of brain, chest, abdomen, and pelvis. Thus, the data suggest that administration of 1A7 can be beneficial to melanoma patients, including in delaying recurrence of melanoma in these patients.

With respect to the Examiner's contention that the specification fails to "enable an antibody that is 'heat-treated' to any unspecified temperature and time and obtains the claimed properties of delaying recurrence or delaying development of melanoma in an individual" (Office Action, page 7), Applicants reiterate the points set forth above in discussing the §112, second paragraph rejection. The specification teaches that a vaccine composition comprising 1A7 can be incubated to, for example, about 48°C. Specification page 54, lines 15-16. Applicants respectfully submit that one skilled in the art would know what temperature(s) would be appropriate in the context of functional embodiments of instant claims 75 and 89, which are directed to a method of delaying recurrence and a method of delaying development of a GD2-associated tumor in an individual, respectively. Indeed, as the Examiner himself stated, "[o]ne skilled in the art would not expect an antibody that was heated to any undetermined temperature such as 100°C or more for an unspecified time to function and bind antigen or produce the claimed properties as . . . encompassed by claims 75 and 89." Office Action, page 7. It is evident, therefore, that one of skill in the art would be able to determine an appropriate heating temperature that would achieve functional embodiments of the claimed methods.

Concerning priority

The Examiner deemed that claims 62-89 have been granted the priority date of application 08/591,196, now U.S. Patent 5,977,316, filed 1/16/96, instead of the priority date of application 08/372,676, now U.S. Patent 5,612,030, filed 1/17/95, allegedly because the limitations of SEQ ID Nos. 2 and 4 are not seen in application 08/372,676.

Applicants respectfully traverse.

Applicants respectfully submit that SEQ ID NOs. 2 and 4 are inherently disclosed in application 08/372,676. SEQ ID NO:2 relates to the amino acid sequence of the light chain variable region of 1A7 and adjoining residues, and SEQ ID NO:4 relates to the amino acid sequence of the heavy chain variable region of 1A7 and adjoining residues. Antibody 1A7 was disclosed in application 08/372,676, as well as the hybridoma producing the 1A7 antibody. A deposit of the hybridoma producing the 1A7 antibody was made as of the filing date of the application under the terms of the Budapest Treaty with the American Type Culture Collection with Accession No. HB-11786 (U.S. Pat. No. 5,612,030, column 5, lines 60-67). As the antibody was disclosed in application 08/372,676, and the hybridoma producing the antibody was disclosed and deposited, the sequences contained within the antibody were also inherently disclosed. Applicants further note the inconsistency in the Examiner's position that Applicants are not entitled to the priority of application 08/372,676, now U.S. Patent 5,612,030, while at the same time citing U.S Patent 5,612,030 as a basis for §103 rejection.

Thus, Applicants respectfully submit that the present claims are entitled to the priority date of application 08/372,676, now U.S. Patent 5,612,030, filed 1/17/95.

Rejection under 35 U.S.C. § 103(a)

A. Claims 76-77 and 82-89 stand rejected as allegedly being unpatentable over Chatterjee et al. (U.S. Patent No. 5,612,030, filed 1/17/95) and further in view of Harlow et al. (Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, pages 96-99, 1988).

Applicants respectfully traverse.

As discussed above, Applicants submit that the present claims are entitled to the priority date of application 08/372,676, now U.S. Patent 5,612,030, which was filed 1/17/95. As one of the cited references, Chatterjee et al., is a priority document for the present application, it does not qualify as art reference under §103(a).

In view of the above, Applicants respectfully request the withdrawal of the instant rejection.

B. Claims 76-77, and 82-89 are rejected as allegedly being unpatentable over Chatterjee et al. (*J. Immunol.* (1993), 150 (8 part 2) 142A Abstract 805) and further in view of Saleh et al. (*J. Immunol.* (1993), 151:3390-3398) and Harlow et al. (Antibodies, A Laboratory Manual, Cold Springs Harbor Laboratory, pages 96-99, 1998).

Applicants respectfully traverse.

Applicants submit that Chatterjee et al. is an inappropriate §103 reference. The Examiner contends that although claim 76 recites an antibody that comprises the light and heavy chain variable region sequences of SEQ ID NO:2 and 4, Chatterjee et al. have produced an anti-idiotypic antibody named 1A7 that is presumably the same as that disclosed in the instant specification. Applicants respectfully submit that Chatterjee et al. do not provide an enabling disclosure with respect to an antibody comprising the light and heavy chain variable region sequences of SEQ ID NO:2 and 4, as they did not disclose these sequences nor was the antibody publicly available at the time of publication of the reference. Because of the uniqueness of the 1A7 antibody in comparison with other antibody molecules, and therefore any antibody comprising the variable region sequences of the 1A7 antibody, the invention may only be practiced:

1. By obtaining the antibody (or the antibody encoding gene) from the 1A7 hybridoma line, which was not publicly available prior to the effective filing date of the present application (priority date as discussed above); or

2. By synthetically producing an antibody with an identical amino acid sequence, which was not publicly disclosed prior to the effective filing date of the present application (priority date as discussed above).

Uniqueness of antibody sequences as a feature of the generation of antibody diversity

Intrinsic to the 1A7 monoclonal antibody is its amino acid sequences; particularly those of the light and heavy chain variable regions. The extreme unpredictability of reproducing the 1A7 monoclonal antibody in a second animal stems from the mechanism by which antibody encoding sequences are formed. This mechanism causes a wide diversity of amino acid sequences for antibodies with similar specificities.

Immunoglobulin heavy chain genes arise in the B cell lineage from rearrangement of about 25-200 variable region genes, about 10 D regions, and about 5 J regions, with the order of 100 splice variants being possible for each D-J combination. Except for the lack of a D region, formation of a complete light chain gene is nearly as complex. Different heavy chains may associate with different light chains. The total number of combinatorial possibilities is therefore of the order of 10^7-10^8.

Only a proprotion of these combinatorial possibilities yield viable antibody molecules with a particular specificity. However, another level of diversification is introduced following gene rearrangement. Antibody-producing B cells which are specific for an immunogen undergo further diversification by deliberate somatic mutation of the rearranged heavy and light chain variable region genes. Some of the results of this mutation process are the emergence of clones with modified specificity, higher affinity, faster forward rate constants, and combinations thereof.

Thus, the possibility of two antibody-producing cell lines from different animals comprising complete identical variable region genes before mutation is remote; the possibility of two such cell lines comprising identically mutated variable region genes is so vanishingly small as to be essentially nil.

Different antibodies recognizing the same target have widely diverse sequences, due to genetic rearrangement followed by mutation. The mutations accumulate as B cells pass through the memory compartment. Amino acid substitutions may occur at nearly any position in the light and heavy chain variable regions, as long as the replacement does not impair specificity. Antibody produced by a clone that has gone through the memory compartment comprises a number of such substitutions. The number of possible sequences for an antibody of any particular specificity is immense.

Uniqueness of the 1A7 sequence

The 1A7 monoclonal antibody was developed by immunizing and selecting with the murine mAb 14G2a. Four immunizations were required to obtain a response, as opposed to the usual requirement of two immunizations for a mature anti-hapten response. Therefore, clones emerging with anti-14G2a specificity have been through the memory compartment and subjected to a period of somatic mutation at least once, and possibly three times.

Accordingly the number of possible sequences for an anti-idiotype antibody with specificity for 14G2a is expected to be large. This is confirmed by sequence analysis and comparison with all known sequence in databases sourced by the National Center for Biotechnology Information using the BLAST alignment algorithm. The results demonstrate that in addition to features generated by gene selection and rearrangement, there are about 16 point differences between 1A7 and the amino acid sequences encoded in the germline genes from which it was derived. The 1A7 light chain differs from the closest amino acid sequences in the prior art in at least two positions within the variable region, and the 1A7 heavy chain differs from the 50 closest amino acid sequences by a minimum of about 14 deletions or insertions, and usually by at least 22 such changes. Particularly significant is the finding that there are about 16 differences between 1A7 and the consensus of the most closely matched sequences.

Furthermore, Blier et al. (*J. Immunol.* (1987), 139:3996) have found that even after gene rearrangement, the sequences of monoclonal antibodies with the same specificity derived from

the same ancestral cell in the same animal still differed substantially from each other. Of course, a practitioner attempting to recreate 1A7 is faced with the challenge of generating it in a different animal. Antibodies obtained from different cells in different animals are even more diverse.

In view of the extensive mutation in 1A7 away from germline sequences, it is essentially impossible for anyone to obtain 1A7, by immunizing a different animal, even using the exact protocol used to obtain 1A7.

Thus, Applicants submit that Chatterjee et al. do not disclose sufficient detail for one skilled in the art to produce an antibody comprising the variable region sequences of 1A7. Applicants further note that this reference was not deemed to be anticipatory under §102 in application 08/372,676, which included claims to the 1A7 antibody, for the reasons outlined above, i.e., the reference was non-enabling, nor was it used as a basis for §103 rejection in that application. Without availability of this primary reference, the instant §103 rejection should be withdrawn.

Applicants also note the inconsistency in the Examiner's position regarding the alleged shortcomings of extrapolating from in vitro studies and animal studies to similar procedures in cancer patients under the §112, 1st paragraph rejection (Office Action, page 6, citing Gura et al.), and the Examiner's reliance on rabbit experiments involving a different anti-idiotype antibody in Saleh et al. as a basis for obviousness. Indeed, Saleh et al. merely show Ab3 production in animals with no disease, and thus do not relate to administration to individuals with melanoma. One skilled in the art would reasonably conclude that evidence obtained in a rabbit model (with no disease) would not correlate with results expected in human patients.

In view of the above, Applicants respectfully request withdrawal of the instant rejection.

C. Claims 76-77 and 82-89 stand rejected as allegedly being unpatentable over Chatterjee et al. (*J. Immunol.* (1993), 150 (8 part 2) 142A Abstract 805) and further in view of

Cheung et al. (*Int. J. Cancer* (1993), 54:499-505) and Harlow et al. (Antibodies, A Laboratory Manual, Clod Springs Harbor Laboratory, pages 96-99, 1988).

Applicants respectfully traverse.

As discussed above under the rejection over Chatterjee et al. (1993) in view of Saleh et al. (1993) and Harlow et al., Chatterjee et al. do not provide an enabling disclosure with respect to an antibody comprising the light and heavy chain variable region sequences of SEQ ID NO:2 and 4, and therefore is not an appropriate §103 art reference. Without availability of this primary reference, the §103 rejection should be withdrawn.

Applicants further note that Cheung et al. disclose a method of inducing anti-GD2 immune response in mice using anti-idiotype antibodies raised against Ab1 antibody 3F8, whereas 1A7 is raised against Ab1 antibody 14G2A. As such, one of skill in the art would expect that the anti-idiotype antibodies raised against these different monoclonal antibodies would contain different variable regions and represent different epitopes of GD2. It is well-established in the art that anti-idiotype antibodies for different epitopes of an antigen may not induce the same immune responses. One of skill in the art would understand that using a method of administration developed for one anti-idiotype antibody does not necessarily extrapolate to another anti-idiotype antibody. Applicants note the inconsistency in the Examiner's position regarding the alleged shortcomings of extrapolating from in vitro studies and animal studies to similar procedures in cancer patients under the §112, 1st paragraph rejection (Office Action, page 6, citing Gura et al.), and the Examiner's reliance on mouse experiments in Cheung et al. as a basis for obviousness. Indeed, Cheung et al. merely show Ab3 production in animals with no disease, and thus do not relate to administration to individuals with melanoma. One skilled in the art would reasonably conclude that evidence obtained in a mouse model (with no disease) would not correlate with results expected in human patients.

In view of the above, Applicants respectfully request withdrawal of the instant rejection.

CONCLUSION

Applicant believes they have addressed all issues raised by the Office and that the claims are in condition for allowance, which is respectfully requested. If the Examiner wishes to discuss this application or provide comments, s/he is invited to telephone Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 304142000201. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: May 29, 2001 By: _____

Paul S. Naik
Limited Recognition Under 37 CFR §10.9(b)
(copy of certificate attached)

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

MONOCLONAL ANTIBODY 1A7 AND USE FOR THE TREATMENT OF MELANOMA AND SMALL CELL CARCINOMA

In the specification

On page 1, the paragraph beginning on line 9, has been amended as follows:

This application is a continuation of U.S. Serial No. 08/752,844, filed November 21, 1996, now U.S. Patent No. 5,935,821, which is a continuation-in-part of U.S. Serial No. 08/591,196, filed January 16, 1996, now U.S. Patent No. 5,977,316, which is a continuation-in-part of U.S. Serial No. 08/372,676, filed January 17, 1995, now U.S. Patent No. 5,612,030, all of which are hereby incorporated herein in their entirety.

On pages 85 and 86, the paragraphs from line 4 on page 85 to line 5 on page 86, containing the paragraphs previously amended in the Preliminary Amendment of April 15, 1999, have been amended as follows:

Amongst the 50 database sequences matched most closely to that of the 1A7 heavy chain variable region, none was identical. The following summarizes the main points deduced from the comparison.

- The closest match was with a heavy chain fragment beginning at residue 9 (designation gp|M36221|MUSIGHAEB_1). There were [**6**] 6 substitutions between residues 1 and 97 (before the VDJ junction), [**6**] 6 substitution differences after residue 97, and 1A7 was shorter about the VDJ junction by [**2**] 2 residues.
- The closest match with a full length heavy chain variable region had the following features (designation gp|U01185|MMU01185): There were [**10**] 10 substitution differences between residues 1 and 97, [**6**] 6 substitutions after residue 97, and 1A7 was shorter about the VDJ junction by [**3**] 3 residues.

- 1A7 differed in length from all sequences but one, due to insertions or deletions of 1 to 8 residues about the VDJ junction. For the sequence of equal length (designation pir|S11106|S11106), there were [**18**] 18 substitution differences between residues 1 and 97, and [**7**] 7 substitutions after residue 97.
- All other comparisons showed at least [**14**] 14 substitution differences between residues 1 and 97.
- All other comparisons showed at least [**3**] 3 substitution differences after residue 97.
- All other comparisons showed a total of at least [**20**] 20 insertions, deletions and substitution differences.
- Differences appeared throughout the variable region.

Amino acid consensus sequences of the 15 most closely matched V_L and V_H regions were designed, and compared with the 1A7 sequences. This is shown in Figure 3(C). Other than splicing differences about the VDJ junction, there appear to be about 15 differences between 1A7 and the prototype sequences. Two of these differences are present in the light chain; 13 are present in the heavy chain. Seven occur in the CDRs, while nine occur in the variable region framework. The point differences likely have arisen from somatic mutation of germline variable region sequences.

In the claims

New claims 90-99 have been added.

BEFORE THE OFFICE OF ENROLLMENT AND DISCIPLINE
UNITED STATE PATENT AND TRADEMARK OFFICE

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Expires: November 29, 2001

Harry I. Moatz
Director of Enrollment and Discipline